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Short Report

Optimizing cervical cancer care in resource-constrained developing countries by tailoring community prevention and clinical management protocol

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ABSTRACT

Cervical cancer is the commonest malignancy among women in resource-poor low- and middle-income countries (LMICs). Western models of health-care organization and delivery may not be suitable for these settings. Research in health services needs to be undertaken before Western oncological prevention and management protocols can be adopted from the innovative affluent countries. It is possible to tailor cervical cancer prevention and management protocols and to avoid inappropriate technology on the basis of a literature review of demographic and clinical profiles in LMICs.

Introduction

Cervical cancer is one of the commonest malignancies and causes of cancer death in less-developed regions of the world, with age-standardized incidence and mortality rates of 17.7 and 9.7 respectively. Every year, more than 80% of new cases and consequent deaths occur in the developing regions of the world. With 134,420 new cervical cancer cases and 72,825 deaths reported by GLOBOCON 2008, India accounts for more than a quarter of the global burden of cervical cancer [1]. A wide variation in incidence rates and differential clinical profiles of cervical cancer between nations and geographical regions suggests a role for environmental factors in etiology, pathogenesis and progression. Human papillomavirus (HPV), poor genital hygiene, patterns of sexual behavior, cultural factors, socio-economic factors (education and income), smoking, and a diet deficient in vitamin A are some of the causal associations and etiological risk factors of cervical cancer. Lower socio-economic status (SES) may be associated with lack of awareness of genital hygiene, indulgence in high-risk sexual activities and subsequent acquisition of sexually transmitted HPV infection, and development of pre-neoplastic changes (dysplasia and cervical intraepithelial neoplasia grades I through III) with gradual progress to invasive cervical cancers (coherence of association) [2]. HPV has occupied a central position in the etio-pathogenesis of cervical cancer since high-risk HPV DNA is consistently identified in formalin-fixed paraffin-embedded tissue specimens, small pre-neoplastic lesions, and also in cervical scrapes (temporal association and specificity of association, consistency of association) [3]. Disruption of the E2 gene of the host caused by integration of HPV DNA in the genome of infected subjects leads to the production of E6 and E7. Accumulation of multiple mutations and cervical cancer are the sequential outcomes of interference of E6 and E7 onco-proteins with the tumor suppressor function of p53 and pRB (biological plausibility) [4]. The germ theory of disease (Koch's postulate) insists that the cause must be both necessary and sufficient for the occurrence of the disease before it can be qualify as the cause of that disease. However, the association between HPV and cervical cancer fails to satisfy the criterion of a one-to-one causal relationship of Koch's postulate, as HPV is a necessary but not a sufficient cause of cervical cancer. Although HPV falls short by the criterion of a direct causal association with cervical cancer, it completely fulfills additional criteria for judging causality, i.e., temporal association, strength of association (higher relative risk of cervical cancer in HPV-infected individuals), specificity of association (further strengthened by the discovery of HPV DNA in malignant neoplasms elsewhere in body), consistency of association, biological plausibility, and coherence of association, thereby firmly establishing HPV as the major contributing factor in the pathogenesis of cervical cancer [2].

Like any other chronic ailment, cervical cancer is also associated with many other risk factors and cofactors. These factors may act additively or synergistically with HPV in cervical carcinogenesis

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(multifactorial association). Other risk factors and cofactors per se may not be carcinogenic in the absence of HPV, and HPV alone may not be a sufficient etiological factor in transforming normal cervical mucosa cells into atypical, dysplastic, pre-neoplastic and invasive cervical cancer cells. Critical biochemical events of the interaction between HPV and other risk factors and cofactors at the cellular level have yet to be elucidated. Emphasis on SES improvement could be a major path-changer in epidemiology, public health and clinical management of cervical cancer, as SES has a bearing on many of the risk factors and cofactors of the disease. Epidemiological studies have demonstrated that cervical cancer incidence and mortality reduce with the advancement of SES, i.e., affluent nations have a lower incidence and mortality as a function of SES [2]. Almost all of the hungry people and one third of 870 million people living below the poverty line live in developing regions of the world, and India may account for >80% and >25% of the global cervical cancer burden (incidence and mortality, respectively) [5]. Incidence and mortality rates have an inverse relationship with socio-economic status even within the confines of territorial boundaries. Incidence, mortality from cervical cancer, and utilization of the Papanicolaou (Pap) smear for early detection of cervical cancer differ across social groups even in developed nations. For example, American black and Hispanic women have a higher risk of developing cervical cancer and are more likely to die of the disease compared to Caucasian (white) women. American women of lower SES are also at risk of missing annual cervical cancer screening cytological examination and consequent early detection of their genital cancers [6,7]. It is very clear from the preceding discussion that SES determines the utilization of preventive oncological services, incidence, pattern, and survival of cervical cancer in economically advanced countries. Lack of adequate health infrastructure, low priority for research, poor documentation, absence of a population-based cancer registry, improper implementation of programs for collection of cancer data and statistics, corruption, social and civil disturbances in low- and middle-income countries, sole focus on treatment of cancer patients with very little emphasis on prevention and early detection, concentration of cancer care resources in metros and city complexes, all contribute to the socio-economic difficulties of people and compromise the optimum management of cervical cancer in economically emerging nations. Unlike the West, developing countries have made very little progress in designing and conducting research enquiring into various issues encountered by cancer patients in accessing anticancer, supportive, palliative and rehabilitation services. The huge burden of disease, the low budgetary allocation for health care, the consumption of a significant amount of resources in managing communicable diseases, mounting social issues of gender violence, crime, corruption, an increasing population, and poverty are responsible for the constantly shifting focus of media, policy-makers and legislators [8–11]. A multitude of social issues are responsible for lack of attention, easy distractibility, disorganization, procrastination and forgetfulness on the part of public health decision-makers. As a consequence, the growing problem of cancer and its prevention and control has not come under the scrutiny of media, policy-makers and legislators in developing countries. Overloading of an already constrained health-care system is the outcome of inequitable distribution of health resources, and many cancer patients die in the community because of poor access to cancer treatment facilities and the unaffordability of expensive anticancer therapy for a large majority of the poor masses [12]. Western models of organization of health-care systems and sophisticated prevention and management protocols of affluent nations have further worsened the scenario. Research and evaluation of prevailing health services in the current socio-economic climate has always been overlooked or, at the most, taken a back seat. Health-system organization, laboratory investigation work-up, therapy schema, follow-up protocols, treatment techniques, cancer management devices and equipment of socio-economically advanced countries have been adopted without extensive subjection of cancer health services to independent and combined pre-adoption or post-adoption evaluation for relevance, adequacy, accessibility, acceptability, effectiveness, efficiency and impact [11].

Socio-economically backward regions of the world have >80% of Earth's population, and this may correspond to 72.80% of the global cases of cancer in these less developed regions [5]. Low- and middle-income countries (LMICs) are also battling population expansion, very low budgetary allocation for health, communicable diseases, insanitation, poverty, corruption, unmet reproductive maternal and child health needs, and lack of universal primary prevention and health-care coverage. Most of the deaths in developing countries are due to infectious diseases, and malnutrition can be prevented by a dedicated and realistic national program. Nevertheless, infectious diseases, malnutrition and maternal and child health continue to claim their toll in spite of the existence of a national health program from as early as 1960s. Under-developed, ill-prepared health-care infrastructure is far from satisfactory to battle even the commonly prevalent and prioritized public health issues [11]. The proportion of chronic illness and death is much higher in higher-income countries than in LMICs. Cancer, globally, kills more people each year than acquired immunodeficiency syndrome (AIDS), malaria and tuberculosis combined. Nevertheless, cancer has hardly found a place in the World Health Organization's list of top ten causes of death, despite the colossal burden of cancer in these economically constrained nations [13]. Another disturbing fact is that the LMICs have to battle 80% of the global cancer burden with just 5% of the total cancer finances [14]. The US spent 17.8% of its GDP of approximately 15.68 trillion USD in the year 2011 for the health care of its people, in sharp contrast to 4.1% of 1.842 trillion USD in the year 2012 [15]. Considering the population of the US to be roughly around one third of that of India, the US spends around 140 times more per capita on health care of Americans compared to that of India. Low health-care spending of LMICs is the consequence of interplay between a number of social/economic/cultural/geopolitical factors, and nothing explains this phenomenon better than the following. Continuously expanding populations, huge dependence on life-subsistence, lower productive traditional occupations, insufficient numbers of technical and higher educational centers to reap the benefit of economic transition and globalization, unemployment, underemployment, a dearth of capital goods such as factories, equipment, machinery and public utilities, ill-equipped and poorly productive labor forces, inability to generate domestic capital or to save substantial amounts of domestic output, and corruption in the form of capital flight to tax havens in economically more advanced countries – all these factors have critically shrunk the financial base of the less developed countries, thereby severely impairing expenditure on public health care [8]. People in immediate need of life-saving medical treatment have to resort to out-of-pocket spending for treatment of their illness. People selling their assets or borrowing money from money-lenders at very high interest rates to pay for treatment of their medical conditions are well documented in India. India also has one of the highest out-of-pocket spending on health in the world, and nearly 5% of the Indian population (39 million people) are pushed into poverty each year by out-of-pocket health-care expenditure. Over the prevailing background socio-economic disadvantages, the health-care system in India is responsible for mounting woes on already distressed families, further disempowering people and trapping future generations into a vicious cycle of poverty because of their health conditions [12,16,17].

It is also very sad that most of the medical journals, irrespective of impact factor, publish articles demonstrating the superiority

Table 1
Evaluation of health services in the context of developing countries: types of cervical cancer screening [20–22].

	Relevance	Adequacy	Accessibility	Effectiveness	Efficiency	Impact	Strength	Weakness	Feasibility
Pap smear	+	–	–	?	+	?	Early stage disease detection	False-positive, un-necessary procedures, increased burden on health budget	–
Liquid-based cytology	+	–	–	?	?	?	Same as above	Same as above	–
VIA/VILI	+	–	–		?	?	Same as above, immediate test results available at the clinic, less resource intensive, as specific as cytology	Less specific than cytology, rest are all same as above	–
HPV testing and genotyping	+	–	–	+	?	?	Identify women at risk of cervical cancer and prevalent HPV type	Lack validation	–

'+' means yes; '–' means no; '?' means questionable, paucity of data.

of the latest technical advancements over conventional practice. Almost all of the opinions, editorials, discussions and debates in both international and national forums, even in developing countries, are on the rapid adoption and implementation of these novel technologies and the phasing out of the well-established robust conventional techniques, without due consideration of the cost-effectiveness and cost-benefits of the planned new techniques and technologies. Most of the implemented new techniques and technologies have not undergone rigorous behavioral and quantitative evaluation of their physical and clinical performances over a required minimum period of time. Developing countries are not far behind in implementing the latest techniques lest they miss the opportunity to harness the due benefits to their cancer patients. At this point, we cannot disagree that the three-dimensional and radio-isotope imaging techniques, tumor markers and multi-leaf-based tele-therapy systems have increased our ability to precisely determine the disease extent, have improved the capacity for prescribing diagnostic investigations and making better clinical decisions regarding the optimal treatment schema, and have decreased the visceral adverse events rates of anticancer therapy (e.g., brain, nasal cavity, lung, breast, prostate, esophagus, stomach, gall-bladder and retroperitoneal tumors). Improvements in staging work-up and therapy capabilities, without doubt, have come from the clinical oncological practice of affluent industrialized Western nations [18]. However, it is worthwhile to note that the US health-care system is criticized as being one of most expensive and inefficient health-care systems in the world [19]. Extrapolating, simulating, adopting Western health-care prevention and services delivery models without validating them in the scenario of developing countries may not be appropriate and can even be counterproductive. In this context, there exists a dire need to evolve models of health-care infrastructural organization and service delivery in LMICs. Cervical cancer being the commonest cancer in the developing world, as well as chronic illnesses that need sophisticated technology for their management, qualifies it as a subject for hypothesizing, designing, developing and testing alternative preventive, initial and follow-up diagnostic work-up, treatment schema, treatment techniques and technologies, supportive and palliative care, follow-up and rehabilitation management protocols.

The objective of this opinion/editorial is to discuss the currently recommended prevention efforts, initial staging baseline pre-therapy work-up and follow-up laboratory investigations, therapy schema, follow-up protocols, treatment techniques (especially those related to radiotherapy) and their clinical results, and available devices and equipment for the treatment of cervical cancer in developing countries. Each of the elements of management of cervical cancer will be described under existing components of evaluation of cancer health services. Strengths, weaknesses and feasibility of commonly employed cervical cancer prevention and management methods and protocols will be deliberated in the following discussion under various headings (Tables 1–7).

Cervical cancer prevention program

Cervical cancer cytology (Pap smear and liquid-based cytology), visual inspection of the cervix using acetic acid/Lugol's iodine (VIA/VILI), and HPV testing and genotyping are some of the prevalent screening techniques [20–22]. Although screening is very useful in detecting early-stage disease and the decrease morbidity and mortality, it is burdensome to health budgets of LMICs, and the benefit of screening has not been replicated in middle-income countries [23].

Clinical examination

Clinical general physical and pelvic examination is the basis of staging of cervical cancer by the FIGO (International Federation of Gynecology and Obstetrics) staging system. The necessity of performing clinical examination cannot be overstated, and it forms the basis for staging the disease, deciding on the therapy schema, imaging and therapeutic techniques and technologies, and determining the need for additional investigations, doses of chemotherapy and portals of radiotherapy [24]. Resource-constrained countries should place stress on maintaining hygiene to avoid the risk of inadvertent transmission of infections.

Baseline laboratory investigations

Laboratory investigations can be divided into hematological, biochemical, pathological, microbiological, endoscopic, electrophysiological, radiological, molecular imaging, and radioisotope studies. These include hemogram, renal function test (RFT), liver function test (LFT), random blood sugar (RBS), serum electrolyte (SE), serology for human immunodeficiency virus (HIV) and hepatitis B surface antigen (HBsAg), chest X-ray (CXR), intravenous pyelography (IVP), barium enema (BE), contrast-enhanced computed tomography (CECT), contrast-enhanced magnetic resonance imaging (CE-MRI), biopsy of cervical lesion, creatinine clearance test (CCT), renal scan, electrocardiograph (ECG), echocardiography (ECHO), multi-gated acquisition scan (MUGA), bone scan, fused

Table 2
Evaluation of health services in the context of developing countries: types of cervical cancer screening (cont.) [20–22].

	Problems in performance	Alternatives	Indications	Contraindications	Yield
Pap smear	Resources intensive, highly trained staff to interpret the results, need for follow-up examination, refusal to accept due to modesty of women, resources for further management of abnormal screen result may be lacking	HPV testing and genotyping alone or in combination with cytology	Test every 3–5 years for Sexually active women from the age of 20–25 years Annual screening if abnormal on prior cytology	Over 65 years of age, no prior sexual encounter, failure to give consent	Sensitivity – 83% Specificity – 98% PPV – 80% NPV – 97.9%
Liquid-based cytology	Same as above	HPV testing and genotyping alone or in combination with cytology	Same as above	Same as above	Sensitivity – 67–95% Specificity – 58–73%
VIA/VILI	Same as above	Same as above	Same as above	Same as above	Sensitivity – 70.8% Specificity – 95% PPV – 62.9% NPV – 96.5%
HPV testing and genotyping	Expensive, rest are all same as above	Cytology screening, visual inspection	Same as above	Same as above	Sensitivity for detecting CIN 3 or higher – 88–91% Specificity for detecting CIN 3 or higher – 73–79%

positron-emission tomography/computed tomography (PET-CT), audiometry, colposcopy, cystoscopy and sigmoidoscopy. Prescriptions for other investigations depend upon pre-existing co-morbid conditions. Routine performance of hemogram, biochemical investigation and cervical biopsy cannot be over-emphasized at this stage of discussion. Cervical cancer is routinely staged by the FIGO staging system. Staging is based on clinical pelvic examination, colposcopy, histopathology, CXR, IVP, cystoscopy and sigmoidoscopy. Imaging and surgical staging are not included in the FIGO staging system as these investigations are not available universally, although FIGO recommends documentation of these findings [24].

Hemogram and biochemistry have to be prescribed both at baseline, weekly, and before administering chemotherapy. Biopsy of the cervical lesion is the basis for diagnosis of cancer; some centers may nevertheless start anticancer therapy based on the findings of a clinical examination. Biopsy of cervical lesions should be insisted upon every time to avoid exposing the patient to the toxicity of anticancer therapy without any benefit. CXR, IVP, BE, renal scan, bone scan, cystoscopy, sigmoidoscopy and audiometry may be reserved for patients with specific symptoms, as routine investigation may yield positive findings in <10% of screened patients against the background of major loss to follow-up [25]. CXR and ECG may be specifically requested by the anesthetist for patients undergoing physical pelvic examination and brachytherapy under anesthesia, and interstitial brachytherapy.

Developing countries are facing an epidemic of diabetes, stroke and coronary artery diseases as a result of increased life expectancy. CCT and renal scan, in addition to detecting a non-functional kidney due to cervical cancer, estimates glomerular filtration rate and subsequent risk of renal failure. However, serum creatinine is the gold standard for detecting renal failure, and obsolete CCT and costly renal scan may not be available in all the centers. Cisplatin is cardiotoxic when it is part of a multi-drug chemotherapy regimen, and it may not be appropriate to get ECG, ECHO, or MUGA when planning single-agent weekly CDDP in patients <50 years of age with no prior history of cardiac disease, or normotensive individuals. Further studies are needed to stratify patients at risk of chemotherapy-induced nephrotoxicity and to identify patients in whom cardiac evaluation can be avoided [11,26].

CECT, CE-MRI, and PET-CT are inferior with respect to detecting parametrial disease and tumors <5 mm that are best appreciated by clinical pelvic examination. Studies demonstrating the superiority of imaging over pelvic examination have failed to comment on vaginal (particularly the lower third) and parametrial extension, i.e., FIGO IIIA and IIIB respectively. More than two thirds of cervical cancers are locally advanced in LMICs, and defining treatment schema and determining radiotherapy portals are based on the clinical stage of the disease [27]. Therefore, three-dimensional imaging may not be appropriate in resource-constrained countries. Imaging also further strains already constrained health budgets, increases waiting time for therapy, and delays the start of anticancer therapy; as a result tumor control is decreases and there may be an increase in drop-out/default of patients before/during therapy respectively [28].

Treatment schema

Surgical techniques are basically used for diagnosis, staging and radical resection of cervical cancer. The standard of care in management of cervical cancer includes conization, simple hysterectomy for FIGO stage IA1 disease, radical hysterectomy/radical trachelectomy with pelvic lymph-node dissection with or without radiotherapy or radiotherapy alone for IA2, IB and IIA, chemoradiotherapy for locally advanced cervical cancer (IIB–IVA), and palliative radiotherapy and/or chemotherapy for stage IVB disease. Cervical cancers are symptomatic in 70–80% of cases, and are locally advanced by the time they present to clinicians as only about 5% of all women in developing countries undergo cancer screening. Patients designated as surgical candidates for radical curative resection form only a small fraction of the colossal burden of cervical cancer. Moreover, comparison of primary surgery with primary radiotherapy in a randomized controlled study of patients with early-stage disease (IB onwards) has shown equal disease-free and overall survival. Hence the primary focus of treatment of cervical cancer is on radio-therapeutic management. Tele-therapy with concurrent weekly cisplatin (CDDP) followed by intra-cavitary (ICBT) or intra-vaginal brachytherapy (IVBT) for radical and postoperative treatment is the current standard of care in the management of cervical cancer. The addition of weekly cisplatin decreases the chances of recurrence, and increases both progression-free survival and overall survival. Brachytherapy is an integral part of radiotherapy management of cervical cancer as the disease control is suboptimal in the event of brachytherapy being skipped [10,24].

Treatment techniques and technologies

Tele-therapy is usually delivered by tele-cobalt (Co-60) or linear accelerator (linac). The International Atomic Energy Agency (IAEA)

Table 3
Evaluation of health services in the context of developing countries: initial and follow-up diagnostic laboratory investigation [24–28].

	Relevance	Adequacy	Accessibility	Effectiveness	Efficiency	Impact	Strength	Weakness	Feasibility
Hemogram	+	+	–	+	+	+	Very sensitive indicator of impact of therapy	Need for weekly test	+
RFT	+	+	–	+	+	+	Same as above	Same as above	+
LFT	+	+	–	+	+	+	Same as above	Same as above	+
RBS	+	+	–	+	+	+	Same as above	Same as above	+
SE	+	+	–	+	+	+	Same as above	Same as above	+
Serology	+	+	–	+	+	+	Identifies virus associated malignancy	Expensive	+
CCT	+	–	–	+	+	+	Determines patients at high-risk of chemotherapy associate renal failure	Obsolete now-a-days	–
Renal scan	+	–	–	+	+	?	Detects non-functioning kidney and patients at high-risk of renal failure	Expensive	–
IVP	+	–	–	+	+	+	Same as above	Risk of contrast reaction	+
CXR	+	+	+	+	+	+	Most basic investigation	<5% of cervical cancer patients have lung metastasis	+
BE	+	–	–	+	+	+	In-expensive	Cumbersome	+
Biopsy	+	–	–	+	+	+	Only basis of diagnosis	Time consuming and painful	+
CECT	–	–	–	–	–	–	Can detect para-aortic lymph nodes and hydro-ureteronephrosis	Expensive, time-consuming, may not truly delineate the disease extent	–
CE-MRI	–	–	–	–	–	–	Same as above	Same as above	–
ECG	Conditional+	+	+	+	+	?	Detects co-morbid conditions	May not be needed if patient is not planned for examination and procedure under anesthesia	+
ECHO	–	–	–	+	?	?	Same as above	May not be needed with single agent cisplatin	-
MUGA	–	–	–	+	?	?	Same as above	Same as above	–
Bone scan	–	–	–	+	?	?	Detects osteoblastic bone metastasis	Cervical cancer rarely throws metastasis to bone	–
PET-CT	–	–	–	?	–	?	Can be useful to detect recurrent/metastatic diseases	Very expensive and its role is still under investigation	–
Audiometry	+	–	–	+	+	+	Determine baseline hearing level	Difficult to find audiometry technicians	–
Colposcopy	+	–	–	+	+	+	Can complement screening efforts	Need technical man-power	–
Cystoscopy	+	–	–	+	+	+	Out-patient (OPD) procedure	Difficulty in maintaining	+
Sigmoidoscopy	+	–	–	+	+	+	Same as above	Same as above	+

Table 4
Evaluation of health services in the context of developing countries: types of cervical cancer screening (cont.) [24–28].

	Problems in performance	Alternatives	Indications
Hemogram	–	–	Baseline and during therapy
RFT	–	–	Same as above
LFT	–	–	Same as above
RBS	–	–	Same as above
SE	–	–	Same as above
Serology	–	–	As screening
CCT	Cumbersome	RFT, renal scan	Baseline
Renal scan	Available only in few centers	RFT	Same as above
IVP	Single non-functioning kidney is very rare	RFT	For FIGO staging
CXR	Exposure to radiation, waiting time		Same as above
BE	Cumbersome	Sigmoidoscopy	Same as above
Biopsy			Basis of diagnosis
CECT	Available in very limited centers	CE-MRI	At the discretion of physician
CE-MRI	Same as above	CECT	Same as above
ECG			Before anesthesia
ECHO	Difficult to access in non-metros		At the discretion of physician
MUGA	Very limited availability	ECHO	Baseline
Bone scan	Same as above	X-ray	To rule out skeletal metastasis in follow-up patients with skeletal symptoms
PET-CT	Same as above	CECT, MRI	Recurrent/metastatic diseases
Audiometry	Same as above		Baseline
Colposcopy	Same as above		To rule out carcinoma in screen positive individuals
Cystoscopy	Same as above		For FIGO staging
Sigmoidoscopy	Same as above	BE	Same as above

panel has concluded that treatment by linac is three to seven times more expensive than that by Co-60. Irradiation with 45 Gy to the whole pelvis, or 40 Gy to the whole pelvis followed by another 10 Gy with mid-line shielding, is prescribed to restrict the pelvic visceral dose to <45 Gy, i.e., the maximum tolerated dose limit of the viscera. Most of the patients with cervical carcinoma are treated with conventional techniques in order to reduce the cost of treatment and waiting time. Placement of radiotherapy portal and treatment execution is done with the help of X-ray or fluoroscopy and Co-60 respectively. Extended-field irradiation (EFRT) of cervical cancer patients to include microscopically positive para-aortic lymph nodes offers a marginal benefit of just 1% gain in overall survival [29].

The various modalities of radiotherapy currently available for radical and palliative treatment of cervical cancer patients include conventional two-/three-/four-field techniques (Conv.RT-2/3/4), three-dimensional conformal radiotherapy (3-D CRT), intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), stereotactic body radiotherapy (SBRT) and proton therapy (PBT). Planning radiotherapy requires imaging to decide the radiation portals and target volume, and to delineate normal tissue. One of several imaging modalities can be used for radiotherapy planning and dosimetry: pelvic X-ray (PXR), fluoroscopy, CECT, CE-MRI and PET-CT are the popular radiotherapy planning imaging techniques and are sparsely scattered across the vast geographic area in developing countries. The X-ray-based conventional Co-60 therapy technique without the use of thermoplastic immobilization is simple to execute, consumes minimal resources, is least labor- and capital-intensive, and is most popular in resource-constrained developing countries. It is an extremely unfortunate situation for cancer control in sub-Saharan African nations, as many of them lack even one tele-therapy unit in their country.

Brachytherapy is a means to escalate dose to primary tumor dose – while avoiding the surrounding normal tissue (bladder, bowel and small intestine) after maximum radiation tolerance of these organs is reached – by placing applicators within the primary tumor. Low-dose-rate (LDR), high-dose-rate (HDR) and interstitial brachytherapy are the different modalities of brachytherapy, and all have been shown to provide equal tumor control and normal tissue toxicity outcome. Arc therapy and IMRT boost are tele-therapy techniques employed for dose escalation in cases where brachytherapy is not feasible of due to lack of resources or anatomical difficulties in placing brachytherapy applicators.

Drop-out from and default for treatment are significant problems with cancer patients in developing countries, so non-compliance with treatment is quiet common. Multiple treatment sessions of HDR brachytherapy are associated with increased rates of drop-out, hence LDR is preferred over HDR (iridium-192 or Co-60) in developing countries. Another disadvantage of HDR-unit-based Ir-192 is the need to change the expensive and labor-intensive radio-isotope every 3–6 months, in contrast to 5 years for the units based on Co-60 [30].

Supportive care

Anticancer therapy is associated with distressing physical symptoms, and good supportive care is an essential part of the management of cancer patients. Supportive care increases treatment compliance rate, quality of life, and survival, and improves the patient–physician relationship while decreasing the distress and discomfort caused by the cancer and its therapy. Pain, nausea, vomiting, mucositis, cystitis, proctitis and skin exfoliation are some of the acute adverse events of anticancer therapy. Almost all acute adverse events can be relieved with inexpensive generic medications [9].

Palliative care and treatment

The World Health Organization (WHO) analgesic step-ladder provides around 80% pain relief among cancer patients. Medicines falling in each step of the WHO analgesic ladder are quite inexpensive. However, strict legal restriction has hampered the availability of many essential drugs such as oral morphine; >80% of cancer patients in developing countries do not have access to morphine, one of the cheapest pain-relieving medications [31]. Less than 10% of patients with cervical carcinoma present with uremia and/or anuria. Such patients may benefit from forced diuresis, ureteral stenting, percutaneous nephrostomy or hemodialysis (interventions to manage uremia). Patients with poor general condition and those unsuitable for protracted toxic anticancer therapy may be offered short-course palliative radiotherapy. Patients with good general condition but with persistent, recurrent and

Table 5
Evaluation of health services in the context of developing countries: techniques and technology for radiotherapy simulation, planning and treatment delivery [24,29].

	Relevance	Adequacy	Accessibility	Effectiveness	Efficiency	Impact	Strength	Weakness	Feasibility
Tele-therapy	+	–	–	+	+	+			+
Weekly CDDP	+	–	–	+	+	+			+
ICBT	+	–	–	+	+	+			+
IVBT	+	–	–	+	+	+			+
EFRT	–	–	–	–	–	–	Included positive para-aortic nodes	More of bowel toxicity and just 1% survival benefit	–
Conv.RT-2	+	–	–	+	+	+	In-expensive	Access difficulty	+
Conv.RT-3	+	–	–	+	+	+	Same as above	Access difficulty, needs body contouring	+
Conv.RT-4	+	–	–	+	+	+	Same as above	Same as above	+
3-D CRT	–	–	–	+	?	+	Anatomic variation is addressed, dosimetry is ascertained, multi-leaf collimators reduces irradiated volume	Resource-intensive	–
IMRT	–	–	–	+	?	?	Same as above	Resource-intensive, increases treatment and waiting time	–
PBT	–	–	–	+	–	?			
PXR	+	–	–	+	+	+	Simple, in-expensive	Time-consuming	+
Fluoroscopy	+	–	–	+	+	+	Same as above	Need for dedicated machine	+
CECT	–	–	–	?	?	?	Can account for anatomic variation	Resource-intensive, may increase waiting-time	–
CE-MRI	–	–	–	?	?	?	Same as above	Same as above	–
PET-CT	–	–	–	?	?	?	Same as above	Same as above	–
Immobilization	–	–	–	?	?	?	Same as above	Same as above	–
LDR	+	–	–	+	+	+	In-expensive, single-session treatment	Manual brachytherapy may expose personnel to radiation	+
HDR	+	–	–	+	+	+	In-expensive, OPD treatment	Multiple fraction may lead to treatment incompliance	+
IBRT	+	–	–	+	+	+	Patients not suitable for ICBT	Surgeon's learning curve	–
Arc	+	–	–	?	?	?	Patients not suitable for brachytherapy	Need for body contour, may not match the results of brachytherapy	+
IMRT boost	+	–	–	?	?	?	Same as above	Expensive, may not match the results of brachytherapy	–
SBRT	–	–	–	?	?	?	Same as above	Same as above	–

Table 6
Evaluation of health services in the context of developing countries: supportive, palliative and follow-up care [9,25,27,28,31,32,34,35].

	Relevance	Adequacy	Accessibility	Effectiveness	Efficiency	Impact	Strength	Weakness	Feasibility
WHO step I	+	+	+	+	+	+	Over-the-counter	Gastric and nephrotoxic	+
WHO step II	+	+	+	+	+	+	Same as above	Nausea	+
WHO step III	+	–	–	+	+	+	One of the cheapest drugs	Strict legal regulation against narcotics	+
Medication for other adverse-event management	+	–	–	+	+	+	Over-the-counter	Available only in tertiary centers	+
Interventions to manage uremia	+	–	–	+	?	?	Facilitates anti-cancer therapy	Some authors are of opinion that un-treated uremia is painless, morbid and deteriorate QoL	+
Palliative chemotherapy	+	–	–	?	?	?	Occasional patients may respond and improve QoL	Expensive and adverse events may deteriorate QoL	+
Palliative radiotherapy	+	–	–	+	+	+	Short-course, improve QoL	25–40% of patients do not have access to radiotherapy	
Palliative/salvage surgery	?	–	–	?	?	?	Patients with small central cervical disease may be cured	Palliative surgery is highly morbid and deteriorate QoL	+
Best supportive care	+	–	–	+	+	+	Patients can be treated at local place with in-expensive medication to improve QoL	Many non-oncological and general practitioners are not aware of it	+
Hospital-based follow-up	+	–	+	+	+	+	Guide improvement of therapy decision-making, provide counseling and management of adverse events	Long-waiting time to meet specialists and travel to cancer center may have resulted in lost to follow-up as high as 70%	+
Community-based follow-up	+	–	–	+	+	+	Provides follow-up care at local place, does not alters overall survival, time for detection of recurrence or satisfaction	This concept in absolutely non-existent in developing countries as general practitioners are not sensitized	+
Follow-up examination	+	–	–	+	+	+	Early detection of local recurrence	Long waiting time to meet oncologist and lost to follow-up	+
Follow-up investigations	+	–	–	?	?	?	Helps to rule out recurrence, metastasis and other non-cancer pathology in symptomatic patients	May have a very low or no yield if done on asymptomatic patients	+
QoL assessment	+	–	–	+	+	+	Facilitates understanding of issues faced by patients and subsequently steer policy-decisions	Time-consuming	+

Table 7
Evaluation of health services in the context of developing countries: health-care and welfare resources.

	Relevance	Adequacy	Accessibility	Effectiveness	Efficiency	Impact	Strength	Weakness	Feasibility
Cancer center	+	–	–	+	+	+		Poor access, expensive and little or no stress on health services research	+
Radiation oncologists	+	–	–	+	+	+		Commercialization of health and education has further aggravated problem of poor access by impoverished people in developing countries	+
Medical Oncologists	+	–	–	+	+	+		Same as above	+
Surgical Oncologists	+	–	–	+	+	+		Same as above	+
Radiologists	+	–	–	+	+	+		Same as above	+
Pathologist	+	–	–	+	+	+		Same as above	+
Anesthetist	+	–	–	+	+	+		Same as above	+
Physiatrist	+	–	–	+	+	+		Same as above	+
Psychologist/Psychiatrist	+	–	–	+	+	+		Same as above	+
Radiotherapy technologists	+	–	–	+	+	+		Same as above	+
Oncology nurses	+	–	–	+	+	+		Same as above	+
Hospital-based MSW	+	–	–	+	+	+		Concentration of professionals in metros and urban areas	+
Community-based MSW	+	–	–	+	+	+		Same as above	+
Lodge/dormitory	+	–	–	?	?	+	Decrease in-direct expenses, provide stay in the vicinity of hospital	Un-hygiene, shortage of room forces patients to take shelters on foot-paths and pavements. Some patients cannot even afford the nominal charges	+
Travel waiver	+	–	+	+	+	+	Reduces in-direct expenses and improve access to therapy	Patients may be using mode of travel other than or in addition to that which offers travel concession. Hence the overall scheme may be inadequate and may not resolve the issue for which it is planned and implemented. i.e. increasing access of patients to cancer centers	+

metastatic disease can be treated with palliative chemotherapy, and local recurrences may be treated with pelvic exenteration. Yet another simple, cheap, widely accepted option is symptomatic management of patients with advanced, persistent, recurrent and metastatic disease for the relief of the distressing terminal illness symptoms (best supportive care) [32].

Follow-up

The importance of follow-up of patients who have completed their therapy cannot be overemphasized. There is no consensus on the frequency of follow-up of post-therapy cervical cancer patients. Molecular imaging techniques – such as PET-CT and bone scan – have been advocated for the detection of disease recurrence. However, their role in evaluating cervical cancer patients is still under active investigation [27]. The majority of treated patients do not return for follow-up examination in developing countries [28]; in this setting local follow-up near the patient's place of origin may be more appropriate without compromising the outcome [33]. Clinical physical examination may be the mainstay of follow-up care of patients, and laboratory studies are restricted to patients with symptoms to rule out recurrence, metastasis and other associated/unrelated pathologies [25,27].

Rehabilitation

Cancer is a life-threatening disease and causes significant impairment of the patient's life from the time of diagnosis, and such impairment persists even after the illness is cured. Patients may face practical problems (child-care, housing, finance, transportation, work/school), family problems (interpersonal relationships), emotional problems, and spiritual problems in addition to physical symptoms and handicaps caused by their illness. Rehabilitation specialists and psychologists may be available only rarely, and much emphasis is placed on the role played by oncologists, paramedics and medical social workers (MSWs). Lodges/dormitories for the duration of the patients' therapy, facilities for travel-charge waivers, and involvement of community health workers in taking care of patients' children are some of the measure that can improve treatment compliance, outcome and quality of life of patients stricken by cancer. In India, travel concessions are available on intercity trains for cancer patients traveling for their cancer treatment. It is very much justified to extend such a concession for travel by roads, metros and local trains, not only during the period of active treatment and follow-up but also for the rest of the life of the debilitated cancer patient [34].

Quality of life (QoL)

Assessment of the extent of deterioration in both immediate and late global QoL of cancer patients owing to the cancer and its therapy is rarely done in resource-constrained developing countries. Patients completely cease sexual activity after the diagnosis of cancer and pelvic radiotherapy. Sterility, loss of libido, frigidity, dyspareunia, and menopausal symptoms caused by the cessation of endocrine functions of the female genital tract are some of the other QoL issues for cervical cancer survivors. QoL assessment is an important part of the management of cervical cancer, but the paucity of resources may not support a QoL program [9].

Health-care financing of cervical cancer

Many social and health welfare schemes exist in developing countries for the treatment of ailments free of cost for people living below the poverty line. However, to benefit from such schemes the presentation of an identification card is necessary (which is non-existent for those in need), lengthy paper work, and a significant delay in starting treatment; drop-out of patients during the waiting period and non-compliance with therapy due to protracted administrative procedures to obtain approval for anticancer treatment from competent authorities also occur. It has been proved beyond doubt that cervical cancer is a disease of the poor and under-privileged, and diagnosis of cervical cancer can be comfortably taken as an index of poverty. Policy makers should realize that there is a dire need to develop a system that provides prompt treatment of cervical cancer at zero cost to the patient, and to arrange instantaneous approval of therapy without the need for identification cards and tedious paperwork after due consideration has been given to background poverty, disadvantage imposed by a disordered health-care system, and disability caused by the disease per se [28,30,34].

Conclusion

Cervical cancer is the commonest malignancy among women in developing countries. Insufficient health-care budget allocation, poverty and corruption are reasons for poor access to the health-care system, and preventive health-care research, medical education and medical statistic infrastructure are poor. Inappropriate planning and execution of health care and the emergence of unrealistic preventive measures and clinical management protocols in developing countries are the consequences of lack of capacity to conduct health-care research on individual diseases and has resulted in the adoption of Western models of health-care services. There is a lot of scope for avoiding resource-consuming investigations and selectively prescribing specific investigations based on clinical symptoms and signs. Planning appropriate treatment techniques and technologies may increase treatment compliance and satisfaction and decrease the cost of therapy and drop-out rates. Screening for cancer prevention may not be feasible in the face of resource-constraint for both screening and subsequent management of abnormal test. Access to palliative care, supportive care, medications and oncology manpower can be increased by lowering regulatory restrictions, increasing public spending and promoting health-services research.

A detection/yield rate of 15% should be used as a cut-off for prescribing or avoiding investigation and deciding the management plan, technique and technology. Yield rates of many investigations may not reach 15% in view of the huge attrition rate of follow-up visits. Cervical growth biopsy plus or minus CXR and ECG, the cheapest treatment schema of cisplatin-based chemo-radiotherapy that is provided free of cost, and inexpensive technology (Co-60 tele-therapy and brachytherapy equipment) are all that is needed for the management of cervical cancer in developing countries. Establishing a facility for the treatment of cervical cancer should be the first step of a multi-phased national cancer control program in developing countries. Concerns about poor documentation and incomplete staging work-up should be weighed against the absence of a population-based cancer registry, the significant default and drop-out rates for anticancer therapy during the waiting period for investigations, and the time for planning sophisticated treatment techniques. Prevailing health scenarios in developing countries are offering an opportunity to policy-makers and health-care professionals to stamp on the lame excuse of resource constraint and make use of circumstances for optimal and efficient treatment of cervical cancer. It may appear overenthusiastic to advocate the avoidance of certain investigations and treatment techniques, but it is worthwhile to try alternative management protocols in an attempt to provide universal oncological care of cervical cancer patients in resource-constrained developing countries.

Conflict of interest

None declared.

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